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PRINCIPLES OF INTERNAL MEDICINE

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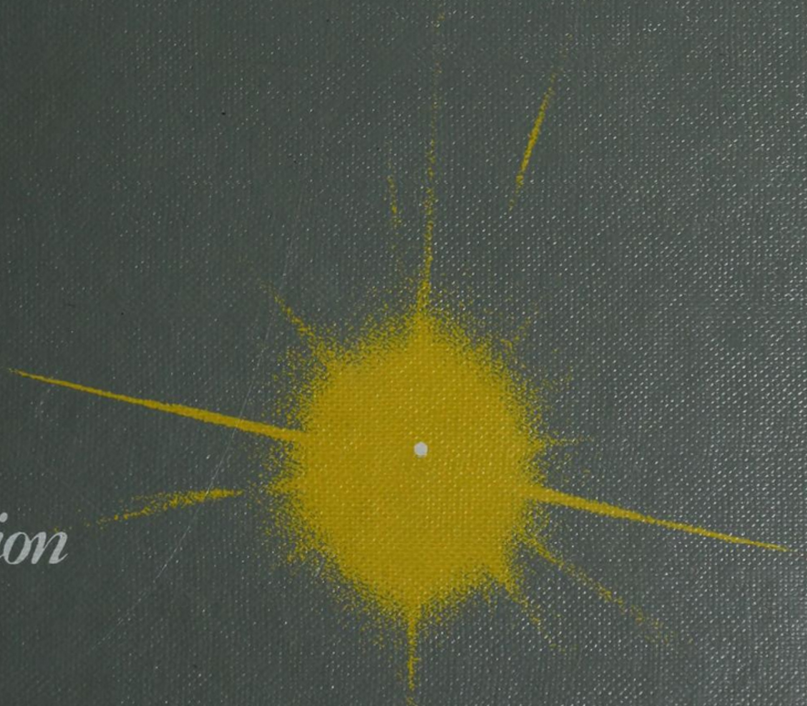

10th Edition

Harrison's

PRINCIPLES OF INTERNAL MEDICINE

Tenth Edition

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giform virus encephalopathies. Although these diseases have been shown to be of infectious etiology by the transmission of neurological illness to higher primates, their causative agents remain incompletely characterized. They are classified as the slow virus infections due to unconventional agents.

SUBACUTE SCLEROSING PANENCEPHALITIS (INCLUSION-BODY ENCEPHALITIS) This progressive and ultimately fatal disease of children and adolescents had been suspected to be of viral origin since its initial description by Dawson in 1932. Measles virus or a virus very closely related to measles virus has been recovered from the brains of patients with the disease. The disorder may be considered to be a slow form of measles encephalitis (see Chap. 200).

SSPE occurs in patients between the ages of 4 and 20; 80 percent are under 11. The disease affects boys 3 to 10 times as frequently as girls. The incidence has fallen recently. Most patients are from rural areas or small towns. Characteristically, they are entirely well until the disease begins. The onset of usually insidious mental deterioration, often expressed by a decline in the patient's schoolwork, is the presenting symptom. Incoordination, ataxia, and myoclonic jerks develop within a few months along with abnormalities of the pyramidal and extrapyramidal motor systems. Cortical blindness, papilledema, and optic atrophy may be present; focal chorioretinitis has been described. A few cases have occurred in association with infectious mononucleosis.

The patient becomes bedridden within 6 to 9 months. Death results from superimposed pulmonary or urinary tract infections or from decubiti. Signs of meningeal irritation are absent.

The CSF gamma-globulin level, as determined by electrophoresis, quantitative immunochemical assay, or colloidal gold curve, is elevated, but the fluid is otherwise normal. The EEG typically shows a "burst suppression" pattern characterized by synchronous and symmetrical spike and high-voltage slow wave activity followed by electrical inactivity. Elevated levels of measles antibody are found in the serum and CSF.

Pathologic findings include lymphocyte and mononuclear infiltrations about small cerebral arteries and veins, intranuclear and intracytoplasmic inclusions in neurons and glial cells, and varying degrees of destruction of medullated nerve fibers. The lesions occur in the cerebral gray and white matter, brainstem and cerebellum.

Measles virus is the etiologic agent. Electron-microscopic studies show that the intranuclear inclusions in brain cells are composed of hollow tubular filaments resembling the internal nucleocapsid component of a paramyxovirus. Staining of brain tissue from patients with the disease demonstrates measles virus antigen in the inclusions. An agent serologically identical with measles virus and having the properties of measles virus has been recovered from brain by cocultivating cell cultures originating from brain tissue with established laboratory cell lines.

Attempts to transmit the disease to animals have met with variable results. Ferrets inoculated with suspensions of brain from patients with the disease develop a nonfatal neurological disorder with EEG changes.

There is evidence that SSPE patients have clinical measles at an unusually early age, but SSPE appears many years after the patient's initial rubeola infection. A few reported cases may have been related to measles vaccination. The risk of SSPE following measles vaccination is far less, however, than the risk of encephalitis or SSPE following natural measles.

SSPE patients lack antibody to one of the measles virus proteins (the M or matrix protein) despite high titers of antibodies to the other viral proteins. The M protein is a nonglycosylated protein localized to the inner surface of the viral membrane; it is important in the assembly of the virus particle at the cell surface. SSPE brain cells do not appear capable of synthesizing the M protein even in normal amounts. The reason for this selective defect in a single viral protein has not been ascertained.

Isoprinosine[1] has been reported by some to affect the course of the disease favorably in an open therapeutic trial, but there is controversy about the drug's effectiveness.

TABLE 360-3
Slow virus diseases of the CNS

Conventional viruses	Subacute sclerosing panencephalitis (SSPE) (inclusion-body encephalitis)
	Progressive multifocal leukoencephalopathy (PML)
	Progressive rubella encephalitis
	Persistent viral disease in immunodeficient patients
Unconventional virus-like agents	Kuru
	Creutzfeldt-Jakob Disease (CJD)
	? Familial Alzheimer's disease

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY This rare neurological condition, first described in 1958, usually occurs in patients who have leukemia, malignant lymphoma, carcinomatosis, immunosuppressive therapy, or a variety of other chronic disease processes. The disease is consistently associated with disorders of cell-mediated immunity with which deficits in humoral antibody response may or may not coexist.

The disease affects adults of both sexes, and its duration from onset of symptoms to death is 1 to 6 or more months. The neurological signs and symptoms reflect a diffuse, asymmetric involvement of the cerebral hemispheres. Hemiplegia, hemianopsia, aphasia or dysarthria, and organic mental changes are frequent; visual field abnormalities and complete or incomplete transverse myelitis may develop. Headache and convulsive seizures are rare, but EEG abnormalities consisting of diffuse or focal abnormalities are often present. Lesions in the white matter may be recognized on CT scans. CSF is normal.

The pathologic changes consist of multiple areas of demyelination with little or no perivascular infiltration and abnormal mitotic figures in astrocytes. The presence of distinctive intranuclear inclusions in oligodendrocytes first suggested that the disease was of a viral etiology. Electron-microscopic observations show the intranuclear inclusion bodies to be composed of closely packed spheres, which have the physical dimensions and properties of the polyomavirus genus of the papovaviruses.

By employing tissue cultures derived from human fetal brain it has been possible to recover a new human polyomavirus serotype (JC virus) from the brains of PML patients. Abundant virus particles are present in brain. Rapid identification of the virus in brain is possible using fluorescent antibody staining or electron-microscopic agglutination with monospecific hyperimmune rabbit serum. Serologic diagnosis using the patient's serum is unreliable. The virus has not been demonstrated in tissues other than brain; the disease has not been transmitted to animals.

There are isolated reports of clinical remission with cytosine arabinoside, but no cures. Death usually occurs within 6 months of onset.

PML may result from the activation of a polyomavirus which has been latent in brain or other tissues since childhood infection. Alternatively, there may be certain individuals who fail to acquire immunity in childhood and have their first encounter with the virus when a disease which interferes with cell-mediated immunity develops. The demyelination which

[1] *This drug has not been approved by the Food and Drug Administration at the time of publication.*